

# The Comparison of Four Weight Reduction Strategies Aimed at Overweight Patients with Diabetes Mellitus: Four-year Follow-up

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Weight change and glycaemic control in 132 diabetic patients previously treated for 1 year by four different methods aimed at weight loss were reanalysed 4 years after the outset. The four treatment groups comprised clinic visits, home visits, behavioural group therapy, and dexfenfluramine given for the initial 3 months followed by clinic visits. When analysed on an intention to treat basis only the dexfenfluramine group maintained a significant weight loss at year 4 (mean  $-2.46$  kg) with 43 % of patients losing 3 kg or more;  $HbA_{1c}$  was not decreased. The other treatment groups showed overall weight regain from year 1 to year 4. Within the home visit group however, the number of patients losing at least 3 kg doubled between years 1 (21 %) and 4 (38 %). When analysed on a completion basis, weight loss in the dexfenfluramine group was significant in females but not in males at year 4. During the 4 years of observation a cohort of 54 patients reflecting our routine clinic practice gained on average 0.35 kg. Although now withdrawn, the use of an appetite suppressant dexfenfluramine for just 3 months would appear to have a long-term advantage on weight loss in this diabetic population, although the weight lost was not associated with improvement in glycaemic control. © 1998 John Wiley & Sons, Ltd.

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## Introduction

We have reported the difficulties of reducing the weight of obese patients with established diabetes mellitus using four defined therapy regimens given for 1 year.<sup>1</sup> The regimens consisted of regular dietetic advice given at the clinic; advice given both at clinic and home; behavioural therapy and dexfenfluramine for 3 months, followed by regular clinic visits. We observed that the dexfenfluramine group lost most weight, although those who completed the behavioural programme did almost as well when assessed at 1 year. Overall, weight loss was disappointing, averaging 3 % or less of the starting weight, and at 1 year there was no consistent benefit to their glycaemic control as measured by  $HbA_{1c}$ .<sup>1</sup> We report here the 4-year follow-up of the patients, in respect of weight and glycaemic control.

## Patients and Methods

### Patients

Insulin-dependent and non-insulin-dependent diabetic males and females aged 16 to 70 years with a body mass index (BMI) of  $28\text{--}45\text{ kg m}^{-2}$  were included in the original study. Any patient who had lost more than 3 kg in weight in the previous year as recorded on the Diabetes Centre computer database was excluded. We chose 3 kg as the exclusion, because audit in our clinic indicates that this represents a significant weight loss for our diabetic population. Pregnant women, patients with unstable thyroid conditions, malignancy, known psychiatric disorders and those on oral corticosteroids were also excluded. Four hundred and nine patients were selected at random and invited to participate in the study. They were contacted by post and asked to reply using a stamped addressed envelope. Two hundred and nine patients (51 %) responded. Of these, 62 patients were excluded; 28 for non-attendance, 22 for weight loss in excess of 3 kg before the start of the study, and 12 for other reasons including malignancy and weight gain resulting in a BMI  $>45\text{ kg m}^{-2}$ . Full informed written

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consent was obtained from all the volunteers and ethical approval was granted by the Tayside Ethical Committee.

### Plan of Study

#### Therapy Groups

One hundred and forty-seven patients suitable for the study were randomized into the following four 1-year treatment regimens:

1. Individual dietetic consultations at the Diabetes Centre (clinic visit group) at 6 weekly intervals for the first 6 months and then 2 monthly for the remainder of the year.
2. Behavioural therapy (behavioural group) involving a physiotherapist and clinical psychologist as well as a dietitian, in groups of up to 10 patients at fortnightly intervals initially for 3 months and then at 2 monthly intervals for the remainder of the year.
3. Individual dietetic consultations at the Diabetic Centre at 6 weekly intervals for the first 6 months and then 2 monthly for the remainder of the year with the addition of dexfenfluramine 15 mg twice per day for the first 3 months (dexfenfluramine group) prescribed by one of us (GL).
4. Individual dietetic consultation combining home and clinic visits (home visit group) at 6 weekly intervals for the first 6 months and then 2 monthly for the remainder of the year. The initial and the fourth visits were in the patient's own home and all the other visits were in the Diabetes Centre.

Details of the type of diabetes treatment (either insulin treated or non-insulin treated) age, sex, and BMI are given in Tables 1 and 2. All patients were seen by the same dietitian during the 1-year study period. The composition of the diet was based on 1992 dietary recommendations:<sup>2</sup> 50–55 % of total energy from carbohydrate, 30–35 % from fat and 10–15 % from protein.

Energy restriction was prescribed according to diet history, weight, sex, age, and physical activity. Further details of the 1-year study and results have been published.<sup>1</sup> At the end of the fourth year, 132 patients were available for study. Nine had died and 6 had become non-attenders.

#### Routine Diabetic Clinic Cohort

A further 58 patients were randomly selected from our computer listings of the diabetic clinic to reflect the routine diabetic service as regards dietetic advice during the initial 1-year study period. Each of these patients had access to a dietitian if they requested or were referred, and had had dietetic advice given when first diagnosed. This cohort reflected the practice at the diabetic clinic at the time of the original study, when only 5 h dietetic time per week was available. From years 2 to 4, a full time (37.5 h per week) dietitian was available for advice if requested or referred. Body weights at outset, year 1 and year 4 were only available for 54 patients in this cohort, as 3 had died and 1 was a persistent non-attender (see Tables 1 and 2).

### Analysis of Data

In addition to the visits to and from the dietitian concerned in this study, all the patients were seen by their usual diabetic clinic doctor at their regular outpatient appointments. Weight measurements were available irrespective of whether the patient completed the defined study group, scale weights were comparable throughout. HbA<sub>1c</sub> was analysed using high pressure liquid chromatography. The data for the four treatment groups were analysed in two ways: on an 'intention to treat' from the outset and on a 'completion' basis for those who completed the planned treatment regimen at 1 year. Comparison was not made statistically on a completion basis with the routine cohort at year 4 as this cohort

Table 1. Weight change on an 'intention to treat' basis

Group	Clinic visit	Behavioural	Dexfenfluramine	Home visits	Routine
Number	32	36	35	29	54
(M:F)	(13:19)	(19:17)	(12:23)	(16:23)	(33:21)
ITDM/NIDDM	9:23	9:27	5:30	12:17	16:38
Age (years)	56.4	58.2	54.5	55	53.3
	52.9, 59.9	55.2, 61.1	51.1, 58.0	50.6, 59.3	50.0, 56.5
BMI (kg m <sup>-2</sup> )	31.8	32.3	32.6	31.8	32.0
	30.6, 33.0	30.6, 34.1	30.3, 34.9	30.5, 33.0	31.1, 33.1
Weight change at 1 year (kg)	-0.99	-1.76	-2.51	-1.59	+1.00
	-2.33, +0.35	-3.41, -0.10	-3.98, -1.04	-2.82, -0.37	+0.23, +1.77
Weight change at 4 years (kg)	+0.24	-0.76	-2.60 <sup>a,b</sup>	-1.00	+0.35
	-1.20, +1.67	-2.42, +0.91	-4.77, -0.43	-2.78, +0.78	-0.84, +1.54
Number deceased	4	0	1	4	3
Number non-attenders	1	2	1	2	1

Mean  $\pm$  95 % confidence intervals.

<sup>a</sup>Weight loss significant  $p = 0.025$  within this group at year four compared to outset weight.

<sup>b</sup>Weight loss significant  $p = <0.05$  for dexfenfluramine group in comparison to clinic visit group.

ITDM, insulin treated diabetes mellitus.

Table 2. Weight change in those completing the study

Group	Clinic visit	Behavioural	Dexfenfluramine	Home visits
Number	20	20	28	23
(M:F)	(9:11)	(11:9)	(10:18)	(15:8)
ITDM/NIDDM	5:15	4:16	5:23	9:14
Age (years)	57.6	58.0	54.9	53.4
	53.3, 61.9	53.9, 62.1	50.8, 59.1	48.2, 58.5
BMI (kg m <sup>-2</sup> )	31.4	32.3	32.0	32.2
	29.7, 33.0	30.8, 33.7	29.3, 34.7	30.8, 33.7
Weight change	-1.88	-2.76	-3.01	-1.71
at 1 year (kg)	-3.73, -0.04	-5.59, +0.07	-4.84, -1.24	-3.08, -0.35
Weight change	-0.48	-0.95	-2.46	-1.92
at 4 years (kg)	-2.24, +1.27	-3.46, +1.56	-4.94, +0.01	-3.85, +0.02
Number deceased	3	0	1	4
Number non-attenders	1	1	1	1

Mean  $\pm$  95 % confidence intervals.

No statistically significant weight changes at year 4 both within and between the group.

had no opportunity for non-completion of a planned regimen. Unpaired and paired *t*-tests, quartile, chi-square and two-way ANOVA were used to compare the data. Mean and 95 % confidence intervals are given.

## Results

### Intention to Treat Analysis

The changes in weight in the four treatment groups after 1 and 4 years are shown in Tables 1 and 2. When analysed on an 'intention to treat' basis, only the dexfenfluramine group showed a significant weight loss after 4 years ( $p=0.025$ ). This group had achieved a mean weight loss of 2.51 kg at the end of the first year and then maintained this advantage achieving a mean weight loss of 2.60 kg by year 4. Within this group, the mean weight loss of the females at year 4 was 4.86 kg ( $p=0.001$ ). The other three groups showed overall no significant weight loss over 4 years, having regained weight lost at the end of the first year. This applied equally for males and females within each of the three groups. Within the clinic visit group, the males showed a significant gain in weight (mean +2.93 kg,  $p=0.005$ ), the females an insignificant loss (-1.61 kg,  $p=0.08$ ). There was also no difference in the weight change at year 4 within any of the four groups when analysed for treatment modality at the outset namely insulin or non-insulin treatment.

The weight loss of the dexfenfluramine group was significantly greater at year 4 compared to both the clinic visit group ( $p<0.05$ ) and the cohort patients ( $p<0.05$ ). During these 4 years the cohort of patients attending our routine diabetic clinic showed no overall weight loss with insignificant mean weight gains of 1.00 kg and 0.35 kg by the end of year 1 and year 4, respectively; there was also no sex difference.

### Completion Analysis

When the data are analysed by 'completion' (Table 2), no group showed any significant weight loss over 4 years and there were no significant weight differences between the groups. However, there were sex differences noted in the clinic visit and dexfenfluramine groups, where the females but not the males showed significant weight losses at year 4. In the dexfenfluramine group the females showed a mean loss of 4.73 kg ( $p=0.005$ ) but the males gained overall 1.62 kg. In the clinic visit group the females lost on average 2.69 kg ( $p=0.03$ ) whereas the males gained 2.2 kg ( $p=0.05$ ).

### Weight Loss of 3 kg or Greater

Table 3 shows the number of patients who lost at least 3 kg at years 1 and 4. On an intention to treat basis, 43 % of those on dexfenfluramine lost 3 kg or more at year 4, a slight increase over the 37 % at year one. Only 16 % achieved this weight loss in the clinic visit group at year 1 and year 4. This goal at 4 years was achieved by more patients in the dexfenfluramine group than the clinic visit group ( $p<0.02$ ). Although overall weight loss (declared above) was disappointing in the behavioural and home visit groups, the number achieving at least 3 kg weight loss improved over the years, especially in the latter group. In the behavioural group the percentage achieving this goal rose from 22 % at year 1 to 33 % at year 4, and from 21 % to 38 % in the home visit group. Achievement of this goal at year 4 was significantly greater in the home visit ( $p<0.05$ ) but not the behavioural group when compared to that observed in the clinic visit group. When analysed on a completion basis, no significances were observed between the groups at year 4 in respect of this goal. In the routine cohort the number achieving a weight loss

Table 3. Number of patients (percentages) who lost at least 3 kg at year 1 and year 4

	Clinic visit	Behavioural	Dexfenfluramine	Home visit	Routine
Intention to treat					
Year 1	5 (16)	8 (22)	13 (37)	6 (21)	4 (7)
Year 4	5 (16)	12 (33)	15 (43) <sup>b</sup>	11 (38) <sup>a</sup>	13 (24)
Completion					
Year 1	3 (15)	6 (30)	13 (46)	4 (14)	
Year 4	4 (20)	6 (30)	13 (46)	8 (35)	

<sup>a</sup> $p \leq 0.05$  for home visit compared to clinic visit groups.<sup>b</sup> $p \leq 0.02$  for dexfenfluramine group compared to clinic visit group.

Table 4. Quartiles for weight change (kg) on an intention to treat basis

	Clinic visit	Behavioural	Dexfenfluramine	Home visit	Routine
Minimum	-8.2	-14.8	-24.7	-12.8	-11
25th percentile	-2	-3.9	-4.7	-3.2	-2
50th percentile	+0.35	+1.1	-2.2	-0.6	-0.5
75th percentile	+2.73	+2.9	+0.3	+1.6	+3
Maximum	+8.6	+9.2	+13.8	+9.5	+13

of at least 3 kg was 4 (7 %) at 1 year and 13 (24 %) at 4 years.

### Quartile Analysis

Weight change is also analysed by quartiles on an intention to treat basis in Table 4. Weight loss was achieved at the 50th percentile for the dexfenfluramine and home visit groups with the most weight loss across the mid range centiles in the dexfenfluramine group (+0.3 to -4.7 kg).

### HbA<sub>1c</sub>

Measurement of HbA<sub>1c</sub> (Table 5) indicated no reduction in any of the groups even in the dexfenfluramine group on an 'intention to treat' or 'completion' basis. Similarly,

HbA<sub>1c</sub> showed no consistent reduction in those who lost 3 kg or more in any of the groups or in those with the greatest quartile loss. In the dexfenfluramine group only two patients had had a change in medication from oral hypoglycaemic tablet to insulin over the 4 years of surveillance. There were no significant changes in HbA<sub>1c</sub> in any of the groups comparing outset with year 4 values.

### Discussion

Previously we have commented on the limited weight loss of our diabetic patients despite intensive efforts using four different treatment regimens. We reported<sup>1</sup> that the 3-month weight loss on dexfenfluramine averaged 3.4 kg (intention to treat) in our diabetic patients and this was no better when weight was remeasured at 1 and 4 years from the outset. Similar low 3-month weight

Table 5. HbA<sub>1c</sub> results

	Clinic visit	Behavioral	Dexfenfluramine	Home visit	Routine
Intention to treat					
At outset	7.70 (4.4, 11.0)	5.97 (2.2, 8.2)	6.28 (4.2, 8.4)	6.72 (3.3, 10.2)	7.02 (3.9, 10.1)
Year 4	7.99 (4.8, 11.2)	6.79 (4.2, 9.4)	7.55 (4.8, 10.3)	7.89 (4.7, 11.1)	7.74 (5.3, 10.2)
Completion					
At outset	7.77 (4.5, 11.1)	6.02 (3.9, 8.1)	6.43 (4.4, 8.5)	6.68 (3.0, 10.4)	
Year 4	8.01 (5.4, 10.6)	6.92 (4.3, 9.6)	7.67 (5.0, 10.3)	7.72 (4.3, 11.2)	

Mean  $\pm$  95 % confidence intervals.

No statistical significant differences between the outset and year 4 values within groups.

loss figures have been reported by others in diabetic patients.<sup>3,4</sup> In the study from Australia reported by Willey *et al.*<sup>3</sup> 34 diabetic patients were randomly assigned to dexfenfluramine or placebo for 12 weeks with weight losses of 3.9 kg on dexfenfluramine and 0.6 kg on placebo. In another 3-month trial of 48 diabetic patients, those on dexfenfluramine lost 3.8 kg and those on placebo gained 0.3 kg.<sup>4</sup> The novel feature of our present study is the subsequent follow-up for a further 3 years, once the 1-year intensive treatment regimens were completed. The interesting finding was the maintenance of the weight loss in those initially given dexfenfluramine for 3 months at the outset. This was noted in both males and females if analysed on an intention to treat basis but only in females on a completion basis. The reason for this weight loss maintenance is unclear and unusual, as in non-diabetic patients weight regain on cessation of dexfenfluramine is the usual reported consequence.<sup>5</sup> Possibly the continued attendance at a Diabetes Centre which re-emphasized dietary adherence played some part in the success of the diabetic patients. If this were the sole explanation, one might have expected the other treatment groups to have maintained the weight lost, which was not the case. Both the clinic visit and the behavioural groups regained most of the weight lost. It should also be noted that within the dexfenfluramine group 43 % of the patients achieved a 3 kg or greater weight loss, far more than in any other group.

Previously we reported the ineffectiveness of home visits to improve weight loss in diabetic patients during the first year of our study.<sup>1</sup> In those patients who completed the study in this group a trend towards maintenance of the weight lost was variable and did not reach significance. Analysis of latest data, however, indicated a doubling in the number who managed to lose at least 3 kg between the first and fourth years, a significant improvement compared to the clinic visit group, suggesting that there may be a sustained long-term beneficial effect. However in the routine cohort of patients who showed no significant overall weight change at year 4 (+0.35 kg), the number who managed to lose 3 kg or more increased from 7 % at the end of the first year to 24 % at the fourth year. This suggests that the Diabetes Clinic's policy of emphasizing dietary adherence which significantly improved with additional dietetic time available after the first year, may indeed be having a beneficial effect. Due to the time and cost of home visits, we would not recommend this form of therapy as cost-effective for the weight lost based on our findings.

The most effective regimen of our four methods therefore included the use of an appetite suppressant, in this case dexfenfluramine, given for a short duration. We have no evidence of the efficacy of long-term usage in diabetic patients due to the licence limitation and this will never be achieved with dexfenfluramine, due to withdrawal of the drug in 1997 following the development of valvular disorders with carcinoid features.<sup>6</sup> Nevertheless the advent of two new agents, namely sibutramine,

a serotonin and noradrenaline re-uptake inhibitor<sup>7</sup> and orlistat, a pancreatic lipase inhibitor,<sup>8</sup> makes drug therapy an option in the future to achieve weight loss. Weight loss at 3 months in non-diabetic subjects on sibutramine (10 mg day<sup>-1</sup>) or orlistat (360 mg day<sup>-1</sup>) is similar to that achieved with dexfenfluramine (30 mg day<sup>-1</sup>)<sup>9</sup> but both are likely to receive longer term usage licences possibly for 2 years and both are effective in diabetic patients.

The lack of change in the HbA<sub>1c</sub> probably reflects the re-establishment of a new state of balance between intake versus expenditure rather than the maintenance of an intake deficit. Such has been described in the UK Prospective Diabetes Study<sup>10</sup> where patients who achieved tight glycaemic control by 3 months dietary weight reduction were followed-up on diet alone for 1 year. Those who maintained the lost weight showed a deterioration in glycaemic control whereas those who managed to maintain tight glycaemic control did so by achieving a further 3 % reduction in weight. Glycaemic control appears to be determined in this situation by the restriction of energy intake rather than the prevailing body weight. In our dexfenfluramine group, weight loss was maintained but not improved, hence the overall upward trend in HbA<sub>1c</sub> values over the 4 years' follow-up. Another factor is that the weight loss was slight, being only 2.9 % in the most successful group, namely those given dexfenfluramine. Others have shown that a 5 % weight loss is required before fasting glucose is significantly reduced whereas a weight loss nearer 10 % is required for a meaningful reduction in HbA<sub>1c</sub>.<sup>11</sup> A 10 kg weight loss in a non-insulin-treated diabetic patient can result in a fall of 30 to 50 % in fasting blood glucose, decrease HbA<sub>1c</sub> by as much as 15 %, and reduce diabetes related mortality by 30 to 40 %.<sup>12,13</sup> Therefore, promotion of longer term weight loss by newer drugs or other means will be required to achieve this goal of 10 % weight loss as recommended by the Scottish Intercollegiate Guidelines Network who have recently reported on obesity management.<sup>14</sup>

In conclusion, inclusion of drug treatment with dexfenfluramine in diet manipulation strategies gave the best weight loss 3 years after the end of an intensive 1-year treatment regimen. Nevertheless the weight loss was slight at 2.9 % and associated with no improvement in glycaemic control and the drug has now been withdrawn. However, consideration should be given to a more aggressive approach to weight management in the diabetes clinic with possible longer term usage of a safer weight reduction drug when such a drug becomes available. It is essential to achieve an improved weight loss if glycaemic control is to be enhanced by weight loss alone.

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